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What can be learned about biology from an engineering perspective?

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Biology has been a very dynamic and successful science in the second half of the twentieth century, thanks to molecular and cell biology methods. However, it seems that the pace of progress is exponentially increasing since the 90s, mostly due to the rise of genomics and functional genomics, which offer radically new ways to investigate cells and organisms (Nowak 1995; Hieter and Boguski 1997). These new technologies have brought about important changes in the way research is conducted. Among these is the necessary development of new collaborative efforts with other scientific disciplines, like physics, mathematics, computer science, and engineering. In this paper, I focus on the calls made in favor of building new bridges between biology and engineering in the context of the emergence of systems and synthetic biology (Csete and Doyle 2002; Lazebnik 2002; Stelling et al. 2004; Tomlin and Axelrod 2005; Endy 2005; Kremling and Saez-Rodriguer 2007; Reeves and Fraser 2009). This issue is interesting because while disciplines like physics and chemistry have played essential roles in the development of modern biology, engineering's contribution has been mainly technical. Here my goal is to discuss the different ways in which engineering methods, models and concepts have been and might be useful in the analysis of biological systems.

Reverse engineering biological complexity

An important part of biology can be conceived as consisting in the analysis of biological systems through a method of decomposition and localization that is fundamentally mechanistic (Bechtel and Richardson 1993; Craver and Darden 2005). Roughly speaking, the goal of such research strategies is to decompose a complex system into its constituent parts and to explain how their interactions produce some

of the system's behaviors. Each component performs a certain operation and through their organization they produce the system's behavior. This is how physiology, cell biology and molecular biology have made great progress in the past. However, the rapid development of new experimental approaches in the last twenty years has shown important limits of classical decomposition methods. It has become evident that the traditional ways used by molecular and cell biologists to build mechanistic models are often not sufficient.

Let me first briefly sketch the nature of these changes. It has begun with the launch of the Human Genome Project and other genomics projects in the 80s. Once complete DNA sequences were known, the real challenge began, because biologists had to find out their functions – what each is doing in the cell's economy. Functional genomics methods have been gradually developed in order to functionally analyze genomic sequences. What is remarkable about the so-called "-omics" approaches is that they allow analyzing cells and organisms at the systems level. What this means is that thousands of components can be observed simultaneously: gene expression (transcriptomics), protein-protein interactions (proteomics), etc. The access to data on a very large scale is of course a great chance, but with it come serious challenges. How to make sense of this flood of data (which are often of relatively poor quality)? How to infer the structure and functioning of the system from these data? How to analyze and explain the properties of these large and complex systems? How to construct mechanistic models with this level of complexity? How to analyze complex dynamical behaviors produced by intricate regulatory mechanisms? It seems that classical mechanistic model building based on intuition is not sufficient. According to many systems biologists, these challenges must be tackled with the help from engineering.

What can be brought by engineering

Because it is often faced with complex system analysis, engineering has developed over the last decades a variety of tools, models and concepts that are potentially helpful for biologists. A first family of methods is called system identification, which basically aims at facilitating inferences about the structure of the system from data

about its behavior (Kremling and Saez-Rodriguez 2007). These data usually come from perturbation experiments. Importantly, these methods can also help design the most informative perturbations experiments. As useful as these methods are, in the case of biological systems, this task is very difficult, and often impossible, for several theoretical and practical reasons. First, because these systems are very large, models would consist of a several thousand ordinary differential equations. Second, the structure is unknown and with potentially millions of parameters, which makes the problem intractable. Third, only a limited amount of relatively poor quality and noisy data is available, which makes the problem even more difficult.

It is thus impossible to start from large-scale experiments and directly retrieve the system's structure. The problem must be constrained, and this can be done in several ways. One of these is to assume that these systems are modular. The modularity hypothesis not only simplifies reverse engineering, but it also plays various kinds of methodological and explanatory roles in systems biology, as we will see. A modular framework has been widely adopted in the last decade in the context of systems biology (Lauffenburger 2000; Segal et al. 2003; Wolf and Arkin 2003). The rationale is that analyzing biological systems in terms of modules is a powerful way to handle their complexity.

Generally speaking, it simplifies the complexity of the task by reducing the number of components and interactions that must be perturbed, measured and analyzed. Instead of studying the interactions between all components (like genes or proteins), several components are grouped into a module and only interactions between modules are modeled. Each module is perturbed and then the intermodular interaction map can be retrieved. An early example of this approach can be found in the work of Kholodenko et al. (2002).

The general underlying principle behind the modular hypothesis is that a module has relatively independent functional properties and can be modeled as an integrated sub-system. In other words, what a module does is relatively independent from the context in which it is embedded. This is a functional criterion, but a module can also be defined structurally, by assuming that intra-modular connections are denser than inter-modular ones. This criterion can be used to identify modules in a large network based only on

structural knowledge. In all cases, the goal is to decompose a large and complex system in terms of relatively small modules, whose properties can be more easily analyzed and described.

There are different ways to carry on such decomposition, depending on how modules are characterized and defined. One approach that has been much discussed recently is based on a comparison of molecular regulatory mechanisms (for example gene regulation networks) with electrical circuits. Such models are particularly interesting, because the comparison with engineering models is direct (and not only metaphorical). In an often-cited paper, Tyson et al. write: "Complex molecular networks, like electrical circuits, seem to be constructed from simpler modules: sets of interacting genes and proteins that carry out specific tasks and can be hooked together by standard linkages… From these components, nature has constructed regulatory networks of great complexity " (Tyson, Chen and Novak 2003).

This quotation encapsulates the most central principles of the modular framework. The first is that each module is characterized by specific dynamic properties that allow it to perform a specific function, in the same way as an amplifier or an oscillator in an electrical circuit. Second, these basic components can be connected in different ways, but according to some rules, and produce new functions and behaviors. Again, this is how many engineering systems are designed. Modules represent standard parts that are used again and again in the building of a large diversity of systems. An engineer who wants to understand the behavior of large circuit does not need to model it at the physical level, because decomposing it in terms of these basic functional modules can explain most of the system properties. It must be stressed that in this framework, the functions are not primarily defined in biological terms or based on chemical properties, but rather in terms of dynamical behavior (oscillator, filter, signal amplification, etc.).

Such method also facilitates hierarchical modeling: modules linked together form higher-level modules. In a landmark paper on this perspective, Hartwell et al. write: "The higher-level properties of cells, such as their ability to integrate information from multiple sources, will be described by the pattern of connections among their functional modules" (Hartwell et al. 1999, C48). This again illustrates how systemic properties are to be explained in this framework.

Importantly, this method of decomposition is different from (though not incompatible with) molecular and cell biology: while the latter focuses on components (genes, proteins, etc.), the modular framework decomposes a system in terms of entities characterized dynamically.

Robert Rosen, a theoretical biologist who worked on dynamical modeling starting in the 70s, had long ago expressed his dissatisfaction with molecular biology's focus on molecular components.

> Thus when we apply a prespecified set of fractionation techniques to an unknown system, there is no reason why the fractions so obtained should be simply related to properties of the original system. Yet this is exactly what happens when a molecular biologist fractionates a cell and attempts to reconstruct its functional properties from the properties of his fractions (Rosen 1972, 54).

He called instead for an analysis based on dynamical properties. Scientists like Rosen remained relatively marginal at that time, but in the last decade a growing number of biologists have been convinced that a new language is necessary to describe and analyze biological systems. There are several reasons to think that engineering can offer such language (Lazebnik 2002). First, it is functional, which is obviously not the case with physics and chemistry. Second, contrary to classical mechanistic models, it deals fundamentally with dynamical phenomena. Engineering is indeed certainly the field that has most successfully developed the cybernetic and systems view originating in the 40s and 50s. Third, it can unify different phenomena through this focus on dynamics, because mechanisms that do not look similar from a molecular point of view can share the same dynamical principles.

Another benefit of adopting an engineering view point is that it provides a kind of *simplicity*, which is much needed, as scientists are increasingly puzzled by the complexity of the systems they study. The complexity of biochemical mechanisms produces relatively simple and reliable behaviors. Models must sometimes be able to ignore part of this complexity and capture these essential features. Molecular biologist's focus on mechanistic details can make them miss these emergent properties. Of course,

this does not mean that detailed and complex models are useless, but only that they must be complemented by the identification of general principles able to provide some intelligibility.

It is to be noted that the emerging field of synthetic biology shows a remarkable convergence with this general view. Whereas classical genetic engineering consists in introducing new genes in organisms, synthetic biologists are interested in rewiring and designing regulatory circuits. A famous example is the repressilator, which is a synthetic gene network designed by Michael Elowitz and Stanislas Leibler (2000) to exhibit stable oscillations. They adopted an engineering perspective in the creation of this new property. Systems and synthetic biology are thus complementary, because while the former focuses on modeling modules and circuits, the latter tries to build them *in vivo*.

Analyzing robustness

Another important contribution of engineering to biology is the study of robustness, understood as the ability of a system to perform a function despite internal and external perturbations (Kitano 2004; Stelling et al. 2004). This is a much-discussed topic since the turn of the century and engineering has contributed to this inquiry in several ways.

The first point is that modularity might be part of the basic architectural requirements for designing a robust system. Kitano writes: "modularity is an effective mechanism for containing perturbations and damage locally to minimize the effects on the whole system" (Kitano 2004, 828). Engineers design their systems to be modular in order to increase robustness. It is not straightforward to find out if biological systems really share this property, but at least biologists have now some tools to address this question.

The second idea is that modules themselves exhibit robustness, at the level of their ability to perform their characteristic function (input-output transformation) or behavior (for example oscillating). The goal is then to measure a system's or a mechanism' s robustness and engineering offers several useful analytical tools, which I can only briefly mention here: sensitivity analysis, which allows a rigorous characterization of the dependency of a dynamical behavior on parameters' values; bifurcation analysis; control analysis.

Another important point is that robustness analysis contributes to the explanation of the complex organization of regulatory circuits. It is probable that in most cases, part of the observed complexity provides the necessary robustness of biological functions (and their relative simplicity at the level of behavior). In other words, many biological functions could be performed with simpler mechanisms, but additional layers of regulation increase their reliability and guarantee that the function is produced despite noise at the level of the components (which is always the case in biological systems). Hence robustness analysis is necessary to understand cellular organization.

The last aspect is more methodological. Robustness analysis provides criteria for model building. The difficulty is that there are always many possible models compatible with experimental data. Robustness analysis can help distinguish between more and less plausible models, because it is unlikely that a non-robust mechanism exists in nature. Of course, this does not mean that the most robust model is the correct one, but this provides some kind of constraint (Morohashi et al. 2002). It can also suggest how to improve a model by identifying which features might increase its robustness.

Conclusion

The modular framework analyzed here looks very convincing and exciting from many points of view. However, some important questions about its fundamental assumptions must be raised. First, can biological systems really be decomposed in such relatively autonomous sub-systems? Second, how good is the analogy with engineering modules?

It is not clear that the identified modules are really independent from other parts of the system. If this dependence is large, the arguments put forward by the proponents of the modular framework become less convincing. This problem also arises in the context of synthetic biology, when it turns out that a designed circuit does not behave in the same way in all cells (because it interferes with normal processes).

It is nonetheless arguable that engineering can offer an original contribution to biology because contrary to physics and chemistry, it shares with biology a functional framework. Engineers have developed a rich set of tools to describe and design

functional devices, based on the rigorous analysis of their dynamical properties. This contribution is not only methodological but also theoretical, as illustrated by robustness analysis. However, there are huge differences between biological and engineering systems. They have tended to be downplayed in the recent hype about these approaches. It is still too early to know how far these analogies can be pushed and how important the transfer of knowledge will be. But the engineering mindset has already encouraged biologists to ask new questions about cells and organisms and explore original avenues of research.

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